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Long-Term Management of Asthma in Children: Safety of Inhaled Corticosteroids

Question

What are the long-term adverse effects of chronic inhaled corticosteroid use in children on the following outcomes?

- ***Vertical growth?***
- ***Bone mineral density (BMD)?***
- ***Ocular toxicity?***
- ***Suppression of adrenal/pituitary axis?***

Summary Answer to the Question

Strong evidence from clinical trials following children for up to 6 years suggests that the use of inhaled corticosteroids at recommended doses does not have long-term, clinically significant, or irreversible effects on any of the outcomes reviewed. Inhaled corticosteroids do improve health outcomes for children with mild or moderate persistent asthma, and the potential but small risk of delayed growth is well balanced by their effectiveness (SRE-Evidence A, B). Updated text is recommended for the EPR-2 incorporating the results of the SRE, but this update does not change the EPR-2 statements.

Rationale for the Question

Inhaled corticosteroids have been proven to be beneficial in the treatment of mild or moderate persistent asthma in children. Because this class of compounds has the potential for producing adverse side effects, however, a SRE on the potential long-term adverse effects would help guide consideration of potential risks and benefits in the therapeutic decisionmaking process.

Systematic Review of the Evidence

The following description of the SRE is an adaptation of the evidence report, including direct excerpts, submitted by the Blue Cross Blue Shield Association Evidence-Based Practice Center. (See Introduction, Methods.)

Methods of Literature Search

To be eligible for consideration in the SRE, each study was required to meet the following criteria:

- It reported on inhaled corticosteroid treatment.
- The treatment duration/observation was at least 1 year.
- For prospective studies:
  - Enrolled only patients younger than 18 years of age.

  OR
  - Stratified outcomes for patients younger than 18 years of age and reported baseline demographics for the stratified subgroup.
- For retrospective studies:
  - Enrolled children and/or young adults younger than 40 years of age and indicated that a substantial proportion of the exposure to inhaled corticosteroids had been during childhood.
  - Study design was a comparative clinical trial, cohort study, case control study, or cross-sectional study.
- Reported on a group of at least 25 evaluable, similarly treated asthma patients per study arm.
- For growth outcomes:
  - Studies of short-term growth were restricted to randomized clinical trials.
  - Studies of long-term growth were restricted to studies that assessed final attained adult height and controlled for confounding variables.
  - For bone density, studies were restricted to controlled trials.
  - For subcapsular cataract, clinical series studies were also included.

- For hypothalamic-pituitary-adrenal (HPA) axis function, studies also were included that used a pre-post single-arm design, where baseline HPA axis function was measured before initiation of inhaled corticosteroids.

Summary of Findings

Studies

The SRE addressed the long-term adverse effects of chronic inhaled corticosteroid use in children on four outcomes: vertical growth; bone mineral density; ocular toxicity, including posterior subcapsular cataract and glaucoma; and suppression of adrenal/pituitary axis. (See the key evidence tables in this section for a description of the studies reviewed for vertical growth [three retrospective cohort/studies on final height]; bone-mineral density [two cross-sectional studies and one randomized controlled trial]; and HPA axis function [six studies, including three randomized controlled trials]). The difficulties of systematically assessing adverse effects are well known. Most clinical trials are not designed to specifically address adverse effects and thus may be statistically underpowered and of insufficient duration to detect long-term adverse effects. In addition, the results of this evidence review do not apply to adults. For the adult population, particularly elderly adults, adverse effects may differ qualitatively and quantitatively. For example, although effects on vertical growth are not a concern for adults, ocular toxicity is likely to occur more frequently as age increases.

Results of Studies

The available evidence suggests that the use of inhaled corticosteroids at recommended doses does not have frequent, clinically significant, or irreversible effects on any of the outcomes reviewed. It is possible that chronic use of inhaled corticosteroids initiated in childhood and continued through adulthood might have cumulative effects that increase the relative risk of certain conditions—such as osteoporosis, cataracts, or glaucoma—in later life. However, none of the available studies had sufficient followup duration or numbers of patients to assess this possibility definitively. It is also likely that the probability of adverse effects is related to inhaled corticosteroids dosage. No studies identified in the published literature, however, were designed to test the dose-response relationship of inhaled corticosteroids to adverse effects.

Vertical Growth

The long-term prospective studies on growth involved budesonide, and the retrospective analyses included studies on beclomethasone, but the results have been generalized to all inhaled corticosteroid preparations. Although different preparations and delivery services may have a systemic effect at different doses, all short-term studies of numerous preparations suggest that the effect of inhaled corticosteroids on growth is a drug class effect.

Evidence addressing three measures of vertical growth in children was found: short-term growth velocity measured over a period of 1 year or less, growth velocity and change in height measured over longer duration (4 to 6 years), and final attained adult height. The evidence on short-term growth velocity is from a published meta-analysis, which pooled data from 5 randomized controlled trials representing 855 subjects, with a mean age of 9.5 years (Sharek and Bergman 2000). Evidence on growth velocity and height over a longer period of time is from the CAMP trial, comparing inhaled corticosteroids (budesonide), nedocromil, and placebo in 1,041 children with mild or moderate persistent asthma, who were followed for 4 to 6 years (CAMP 2000). For final attained adult height, evidence is from three retrospective cohort studies that adjusted for the potential confounding factor of parental height (Agertoft and Pedersen 2000; Silverstein et al. 1997; Van Bever et al. 1999). Together, these three studies included a total of 243 patients with asthma treated with inhaled corticosteroids, 154 asthmatic patients who had not been treated with inhaled corticosteroids, and 204 nonasthmatic controls.

Evidence on growth velocity when evaluated during the first year of therapy is consistent in showing a difference in height averaging approximately 1 cm between children treated with inhaled corticosteroids and controls. The magnitude of this change in height (≈0.5→1.5 cm) has varied between studies using different inhaled corticosteroid preparations, indicating that either the study design or specific steroid preparation/

dose may be important considerations (Doull et al. 1995; Allen et al. 1998; Verberne et al. 1997). In the only trial extending beyond 1 year (CAMP 2000), a difference consistent with this magnitude also occurred during the first year of the study. However, in subsequent long-term followup, the difference in growth velocity was not maintained; all groups had similar growth velocity at the end of treatment. At the end of the 4- to 6-year treatment period, there was still an approximately 1 cm difference in cumulative growth between the study groups, but a slight difference in bone age suggests the potential for catchup for the inhaled corticosteroid group.

The evidence on final adult height appears to be fairly consistent as well. However, this evidence is based on cohort studies that are subject to selection bias and the confounding effects of severity of asthma cannot be adjusted. Some comparisons in these studies also were limited by small sample size. Of the three studies, two showed no difference, and one showed a difference in final attained adult height between inhaled corticosteroid users and nonusers. However, the difference was much less than would be expected if a 1 cm/year growth velocity difference noted in the 1-year studies were maintained over several years.

Bone Mineral Density

The CAMP study followed children with mild or moderate persistent asthma and a mean age of approximately 9 years who were treated for 4 to 6 years with inhaled corticosteroids. This study, with large numbers, randomization, and assessment of longitudinal changes, provides strong evidence that there is no effect of inhaled corticosteroids on bone mineral density (BMD) in the doses given and in the duration in the study (CAMP 2002). One retrospective study of 30 young adults found a significant correlation between BMD and dose of inhaled corticosteroids among female patients (Ip et al. 1994). Such studies are subject to potential confounding because of unmeasured differences between groups that are risk factors for low BMD. In addition, the clinical significance of any observed differences in BMD are unknown. Subtle differences in BMD would not have a clinical impact until they were added to other risk factors such as aging, and it is uncertain whether differences observed during young adulthood would persist into old age.

Posterior Subcapsular Cataract and Glaucoma

Studies that report on the occurrence of posterior subcapsular cataracts consist mostly of small cohorts and cross-sectional studies (Allen et al. 1998; Tinkelman et al. 1993; Agertoft et al. 1998; Simons et al. 1993; Nassif et al. 1987; Abuekteish et al. 1995), with the exception of the CAMP study. The expected incidence rate of subcapsular cataract in any population of normal young children and adults is none. These studies are sufficient to rule out a large effect of inhaled corticosteroids on the short-term incidence of cataract, but they are not capable of detecting a small increase in risk of an event that has a baseline risk of essentially zero. In addition, several of the clinical trials that evaluated development of cataracts were of relatively short duration.

Two of these studies also reported on measurements of ocular pressure (Tinkelman et al. 1993; Nassif et al. 1987). The limited data available show no relationship between glaucoma or increased intraocular pressure and inhaled corticosteroids.

Effect on Hypothalamic-Pituitary-Adrenal Axis Function

Two types of evidence on the effects of inhaled corticosteroids on HPA axis function have been reported: three case reports of iatrogenic Cushing syndrome that were possibly related to inhaled corticosteroids (Zimmerman et al. 1998; Taylor et al. 1999; Priftis et al. 1991; Hollman and Allen 1988) and six controlled clinical trials regarding HPA axis function (Tinkelman et al. 1993; Nassif et al. 1987; Scott and Skoner 1999; Ribeiro 1993; Price et al. 1997; Gonzalez Perez-Yarza et al. 1996). Each study evaluated from one to three different measures of HPA axis function, with followup for at least 1 year after initiation of treatment.

The case reports show that systemic effects can occur in clinically detectable ways, with a strong case for causality indicated in the case studies by the accompanying laboratory tests and response when inhaled corticosteroids were withdrawn.

In the controlled clinical studies, four studies of serum control values identified no differences. However, three other studies used more sensitive tests of cortisol, such as 24-hour urinary cortisol, and two showed a statistically significant effect of inhaled corticosteroids. It should be noted that these statistically significant results occur as comparisons of mean values between groups. Few or no patients in most studies produce laboratory values out of the normal range. However, the clinical significance of these more sensitive indicators of adrenal function is unknown.

The results of the case reports appear to be causally attributable to inhaled corticosteroids based on clinical presentation, consistency with laboratory findings, and clinical response to reduction or withdrawal of treatment. Although the studies show that, on average, persons may only have clinically insignificant effects of inhaled corticosteroids on the HPA axis, some individuals may be acutely susceptible to their effects.

Additional Literature/Information

Since the release of the EPR-2, a FDA-based committee convened to review the safety of inhaled corticosteroid therapy, with particular emphasis on growth effects. The FDA committee recommended inserting the following cautionary wording in package inserts for all (both nasal and oral) inhaled corticosteroid medications: "A reduction in growth velocity in children or teenagers may occur as a result of inadequate control of chronic diseases such as asthma or from use of corticosteroids for treatment. Physicians should follow closely the growth of adolescents taking corticosteroids by any route and weigh the benefits of corticosteroid therapy and asthma control against the possibility of growth suppression if an adolescent's growth appears slowed (http://www.fda.gov)."

Two additional studies on the effect of inhaled corticosteroids were completed after the SRE; the studies involved primarily adults but included some children and thus were considered by the Expert Panel. One report pertaining to the risk of cataract formation among patients 3 to 90 years of age was based on a large retrospective cohort study in the United Kingdom-based General Practice Research Database population, with a nested case-control analysis among users of inhaled corticosteroids and patients without previous steroid use who were younger than 90 years of age. All users of inhaled corticosteroids were at a marginally increased risk of cataract formation (risk ratio = 1.3) compared to patients who did not use corticosteroids. Among individuals 40 years of age or older, the risk ratio increased as numbers of inhaled corticosteroid prescriptions increased after controlling for other variables. These trends were not evident for those individuals younger than 40 years of age (Jick et al. 2001).

A prospective cohort study on bone loss in women 18 to 45 years of age reported that bone-density loss at the total hip and the trochanter—but not at the femoral neck or spine—increased with the number of puffs per day of an inhaled corticosteroid (Israel et al. 2001). However, the clinical significance of these findings is uncertain because the rate of loss reported was small, any association of this small loss with increased risk of bone fracture has not been established, and the rates varied among the women taking the inhaled corticosteroids.

Recommendations for EPR-2

Based on this information from the SRE and additional studies, the Expert Panel recommends the following text (the blue text indicates new text) as an update to pages 71 through 73 of EPR-2 (The Medications, Special Issues on Safety, Systemic Adverse Effects). This text updates—but does not change—the EPR-2 recommendations.

Linear Growth

A reduction in growth velocity in children or adolescents may occur as a result of inadequate control of chronic diseases such as asthma or from the use of corticosteroids for treatment. Overall, however, the available cumulative data in children suggest that, although low-to-medium doses of inhaled corticosteroids may have the potential of decreasing growth velocity, the effects are small, nonprogressive, and may be reversible (SRE-Evidence A, B, C).

The long-term prospective studies on growth involved budesonide, and the retrospective analyses included studies on beclomethasone, but the results have been generalized to incl[illegible] all inhaled corticosteroid preparations. A[illegible]rent preparations and delivery de[illegible]nic effect at different [illegible]es on numerous preparat[illegible] that[illegible]ct of inhaled [illegible]rticosteroids o[illegible] drug-class effect. When [illegible]igh doses of inha[illegible]osteroi[illegible] necessary to [illegible]ieve satisfact[illegible]ma c[illegible]se of adjunctive long-term-co[illegible] th[illegible]iated in order [illegible]educe the d[illegible]ed corticosteroids and th[illegible]inimize poss[illegible] dose-relate[illegible] effects o[illegible]th. Physicians shou[illegible] th[illegible] growth of c[illegible]n and adolesce[illegible]g cortic[illegible] steroids by a[illegible]e and weigh[illegible]enefits of corticosteroid the[illegible] and asthma[illegible]ainst the possibility of growth [illegible]pression o[illegible] chi[illegible] or an adolescent's gro[illegible]th appears slowed.

Bone Mineral Density

Low-to-medium doses of inhaled [illegible]icosteroids appear to have no serious adverse [illegible]ects on BMD in children (SRE-Evidence A) (CA[illegible]P 2000). A small, dose-dependent reduction i[illegible]D may be associated with inhaled corticostero[illegible] in patients older than 18 years of age (SRE-[illegible]idence C; Evidence B) (Ip et al. 1994; Israel et al. 2[illegible] but the clinical significance of these findings is not [illegible]ar

Cataracts

In children, low-to-medium dose inhaled corticosteroid therapy has no significant effects on the incidence of subcapsular cataracts or glaucoma (SRE-Evidence A, C) (CAMP 2000; Jick et al. 2001). High (greater than 2000 mg) cumulative lifetime doses of inhaled corticosteroids may increase slightly the prevalence of cataracts as suggested in two retrospective studies of adult and elderly patients (SRE-Evidence C; Evidence C) (Cumming et al. 1997; Jick et al. 2001).

Hypothalamic-Pituitary-Adrenal Axis Function

The available evidence indicates that, on average, children may experience only clinically insignificant, if an[illegible]ffects of low-to-medium dose inhaled c[illegible]roids on the HPA axis (SRE-Evidence A, [illegible]e individuals, however, may be more susceptible to their effects even at conventional doses.

[illegible]mendations for Future Research

- What are the long-term effects of inhaled corticosteroid therapy on BMD and cataract formation if it is initiated at a young age and continued for prolonged periods of time?
- Are potential growth effects of inhaled corticosteroid therapy more pronounced during certain developmental periods (e.g., first 3 years of life, preadolescence)?

Key Evidence Tables

Table 1-3. Differences in Adult Target Height in Cohort Studies

Study	Group (n) Co	Difference in (Adult Target) Height (cm)[1]
Silverstein, Yunginger, Reed et al. 1997	All asthmatics (n = 153) vs. nonasthmatics (n = 153)	0.2
	All corticosteroid users (n = 58) vs. noncorticosteroid asthmatics (n = 95)	-1.2
	Males: All corticosteroid users (n = 30) vs. noncorticosteroid asthmatics (n = 45)	-1.8
	Females: All corticosteroid users (n = 28) vs. noncorticosteroid asthmatics (n = 50)	-0.8
	Oral corticosteroid users (n = 40) vs. never used corticosteroids (n = 95)	-1.4
	Inhaled corticosteroid users (n = 18) vs. never used corticosteroids (n = 95)	-0.9
Van Bever, Desager, Lijssens et al. 1999	All inhaled corticosteroid users (n = 43) vs. never used corticosteroids (n = 42)	-2.54[2]
	Males: Inhaled corticosteroid users (n = 23) vs. never used corticosteroids (n = 26)	-3.09[2]
	Females: Inhaled corticosteroid users (n = 20) vs. never used corticosteroids (n = 16)	-1.99
Agertoft and Pedersen 2000	All inhaled corticosteroid users (n = 142) vs. noncorticosteroid using asthmatics (n = 18)	+0.5
	All inhaled corticosteroid users (n = 142) vs. healthy sibling control group (n = 51)	-0.6
	Males: All inhaled corticosteroid users (n = 86) vs. healthy sibling control group (n = 24)	-0.6
	Females: All inhaled corticosteroid users (n = 56) vs. healthy sibling control group (n = 27)	-0.8

[1] A negative number indicates that corticosteroid users had lower attained adult height than the comparison group, controlling for parental height.

[2] $p < 0.05$

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44. AHRQ Publication No. 01-E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Table 1-4. Effects of Inhaled Corticosteroids on Bone Mineral Density

Citation	Treatment	Number Enrolled	Number Evaluable	Treatment Duration (years)	Bone	P Value	Comment
Agertoft, Larsen, and Pedersen 1998	Budesonide 504 mcg per day	157	157	3.0 (minimum)	Total body BMD: 0.92 g/cm²		No significant difference between groups or between boys and girls in bone mineral capacity or total bone calcium
	Nonsteroid asthma therapies	111	111	3.0 (minimum)	Total body BMD: 0.92 g/cm²	NS	Mean treatment time 4.4 (3–6) years
Ip, Lam, Yam, et al. 1994	Beclomethasone or budesonide	30	30	3.3	Spine: 0.944	0.041	Stratified by sex, all differences significant for females but not for males
					Femur Neck: 0.769	0.007	
					Trochanter: 0.676	0.034	
					Ward's Triangle: 0.729	0.016	
	Normal control subjects, matched by sex, age, BMI, menopausal status	30	30	NA	Spine: 1.011		
					Femur Neck: 0.835		
					Trochanter: 0.724		
					Ward's Triangle: 0.729		
Childhood Asthma Management Program Research Group 2000a	Budesonide 400 mcg/day	311	311	4–6	Change in spine BMD: 0.17 g/cm²	0.53 vs. placebo	
	Nedocromil 16 mg/day	312	312	4–6	Change in spine BMD: 0.17 g/cm²	0.15 vs. placebo	
	Placebo	418	418	4–6	Change in spine BMD: 0.18 g/cm²		

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44. AHRQ Publication No. 01-E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Table 1-5. Effects of Inhaled Corticosteroids on HPA Function

Citation	Treatment Arms	Measure of HPA Axis Function	
Randomized Clinical Trials			
Scott and Skoner 1999	BUD 500 mcg/day (n = 132) vs. conventional treatment (n = 57)	Serum cortisol at baseline and 12 mo. ACTH-stimulated cortisol at baseline and 12 mo. Percentage of patients from normal to abnormal stimulation test between baseline and 12 mo.	
Price, Russell, Hindmarsh et al. 1997	FP 50 mcg/day (n = 36) vs. cromolyn 20 mg/day (n = 27)	Urinary cortisol geometric mean ratio between patient groups at 6 and 12 mo.	
Tinkelman, Reed, Nelson et al. 1993	BDP 84 mcg/day (n = 102) vs. theophylline (n = 93)	Serum cortisol at baseline, 6 and 12 mo. ACTH-stimulated cortisol at baseline, 6 and 12 mo.	
Cross-Section Studies			
Gonzales Perez-Yarza, Mintegui, Garmendia et al. 1996	Budesonide or beclomethasone mean dose 676 +/- 280 mcg/day (range, 226–1800) (n = 250) vs. normal controls (n = 108)	Urinary cortisol Number of abnormal ACTH stimulation tests in subset with urinary cortisols below 1 standard deviation	
Nassif, Weinberger, Sherman et al. 1987	Beclomethasone 358 mcg/day (n = 17) vs. Beclomethasone 726 mcg/day (n = 14) vs. asthmatic control group (n = 20) and normal control groups (n = 21)	Serum cortisol Urinary cortisol	
Single Arm Pre-Post Study			
Ribiero 1993	Budesonide 200 mcg/day (n = 47)	Serum cortisol at baseline and 12 mo. ACTH-stimulated cortisol at baseline and 12 mo.	

	Results	P Value	Comments
	BUD (0, 12 mo): 320, 300 Conventional (0, 12 mo.): 250, 315	"No significant differences"	Subset of full trial
	BUD (0, 12 mo.): 695, 655 Conventional (0, 12 mo.): 690, 720	"No significant differences"	Subset of full trial
	BUD: 24% Conventional: 21%	"Not different"	
	Ratio of urinary cortisol at 6 mo.: 0.85 Ratio of urinary cortisol at 12 mo.: 0.96	NS: 95% CI includes 1 NS: 95% CI includes 1	
	BDP 336 mcg/day (0, 6, 12 mo.): 328, 306, 309 Theophylline (0, 6, 12 mo.): 309, 322, 334	Not stated: "similar"	
	BDP 336 mcg/day (baseline): 726 (6, 12 mo. NA) Theophylline (baseline): 723 (6, 12 mo. NA)	Not stated: "almost identical"	
	BUD/BDP: 58.69 nmol/m_2/day Control: 81.98 nmol/m_2/day	p <0.05	
	BUD/BDP group: 2 abnormal tests (3.1%) Control group: Not done	Not applicable	One of the two patients with abnormal test had chronic oral corticosteroids.
	BDP <450 mcg/day: 403 BDP >450 mcg/day: 353 Asthmatic controls: 353 Normal controls: 367	Not specifically stated: presumed NOT statistically significant	
	BDP <450 mcg/day: 22 mcg/g creatinine BDP >450 mcg/day: 16.5 mcg/g creatinine Asthmatic controls: 43 mcg/g creatinine Normal controls: 29.5 mcg/g creatinine	Text: "Statistically significant" from controls	
	Basal cortisol (0, 12 mo.): 497, 497	Not stated, presumed not statistically significant	
	4-hr. stimulated cortisol (0, 12 mo.): 1104, 1131 5-hr. stimulated cortisol (0, 12 mo.): 1242, 1380	p = 0.02 for increase from baseline, both tests	

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44. AHRQ Publication No. 01–E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

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Combination Therapy: Addition of Other Long-Term-Control Medications to Inhaled Corticosteroids

Question

In patients with moderate persistent asthma who are receiving inhaled corticosteroids, does addition of another long-term-control agent improve outcomes?

Summary Answer to Question

Strong evidence consistently indicates that long-acting inhaled beta$_2$-agonists added to low-to-medium-dose inhaled corticosteroids improve outcomes (SRE-Evidence A). Adding a leukotriene modifier or theophylline to inhaled corticosteroids or doubling the dose of inhaled corticosteroids also improves outcomes, but the evidence is not as substantial (SRE-Evidence B). The EPR-2 recommendations for moderate persistent asthma have been revised: The preferred treatment for adults and children older than 5 years of age is the addition of long-acting inhaled beta$_2$-agonists to low-to-medium-doses of inhaled corticosteroids. Adjunctive therapy combinations have not been studied in children younger than 5 years of age. For this age group, it is the opinion of the Expert Panel that there are two preferred options for treating moderate asthma: either the addition of long-acting inhaled beta$_2$-agonists to a low dose of inhaled corticosteroids or medium-dose inhaled corticosteroids as monotherapy.

Rationale for the Question

There are an increased number of studies evaluating combination therapy primarily as a result of the development of fixed-dose combinations of the long-acting inhaled beta$_2$-agonists and inhaled corticosteroids (salmeterol plus fluticasone propionate, now FDA-approved, and formoterol plus budesonide, under development). The ongoing preference to minimize the dose of corticosteroids, especially for patients taking high doses, and to reduce the possibility of adverse side effects, has stimulated studies of adjunctive therapies. The question of interest is whether, for patients requiring more than low doses of inhaled corticosteroids, equal or better asthma control could be achieved by adding an additional medication rather than by increasing the dose of inhaled corticosteroids. An extensive body of literature addressing the question of adjunctive therapy has become available since the publication of EPR-2 and has thus warranted Expert Panel Review.

Systematic Review of the Evidence

The following description of the SRE is an adaptation of the evidence report, including direct excerpts, submitted by the Blue Cross Blue Shield Association Evidence-Based Practice Center. (See Introduction, Methods.)

Methods of Literature Search

The SRE divided the studies into three study design categories:

1. The addition of a long-term-control medication to a fixed dose of inhaled corticosteroids compared with the same dose of inhaled corticosteroids alone. This design simply assesses whether combination therapy is better than monotherapy with inhaled corticosteroids. The potential bias from this study design is seen when patients can be controlled on inhaled corticosteroids alone, resulting in a negative study because of the inability to improve.
2. The addition of a long-term-control medication to inhaled corticosteroids with subsequent downward titration of the dose of inhaled corticosteroids to the lowest dose that maintains control. This design is even more problematic because it may be raising a fundamentally different question—i.e., "Can the other long-term-control medication act as a substitute for the inhaled corticosteroids following initial control of the asthma?" However, if the goal is simply to lower the dose of inhaled corticosteroids by some increment (usually half), then the study design addresses the primary question more directly.

3. The addition of the long-term-control medication compared with increasing the dose of inhaled corticosteroids to improve asthma control. This design most directly addresses the question, because eligible patients first demonstrated a lack of adequate control during an open run-in period on inhaled corticosteroids. The definition of inadequate control varied among studies, however, and this variance could introduce some bias.

In addition to the eligibility criteria for selecting studies related to all topics in the SRE (described in the Introduction), the criteria for selecting studies for this question were as follows:

- Study comparisons included:
  - Inhaled corticosteroids alone compared to inhaled corticosteroids plus leukotriene modifiers, or long-acting $beta_2$-agonists, or theophylline

  OR
  - Two different long-term-control medications in patients using inhaled corticosteroids

  OR
  - The addition of an alternative medication to an increased dose of inhaled corticosteroids for patients already on inhaled corticosteroids.
- Treatment duration was at least 4 weeks.
- At least 90 percent of patients in the study were on inhaled corticosteroids, or the subgroup of patients on inhaled corticosteroids was analyzed separately, and this subgroup otherwise met the eligibility criteria for this question.
- No more than 10 percent of the patients in the population or in a subgroup were on oral corticosteroids.

Summary of Findings

Studies

The majority of the studies reviewed by the SRE fit into study design categories 1 and 3. Thirty-nine studies involving 45 comparisons and a total of 9,020 patients were selected for the SRE. (See the key evidence tables in this section.) Overall, 34 of the 45 comparisons evaluated the addition of a long-acting $beta_2$-agonist to inhaled corticosteroids. All but one of the studies were randomized trials. The following comparisons were made:

- Twenty-six compared the addition of a drug to a fixed dose of inhaled corticosteroids (18 [3,163 patients] compared long-acting inhaled $beta_2$-agonists; 4 [234 patients] compared theophylline; and 4 [885 patients] compared LTRAs).
- Four compared a titrated dose of inhaled corticosteroids after the addition of a drug (3 [268 patients] compared long-acting inhaled $beta_2$-agonists; 1 [226 patients] compared LTRA).
- Fifteen compared a low-to-moderate dose of inhaled corticosteroids with an additional drug to high-dose inhaled corticosteroids (13 [4,285 patients] compared long-acting inhaled $beta_2$-agonists and 2 [252 patients] compared theophylline).
- No studies were found that compared long-acting oral $beta_2$-agonists.
- No studies meeting SRE quality criteria were found that compared the addition of cromolyn or nedocromil.

Results of Studies

Addition of long-acting inhaled $beta_2$-agonists

A sufficient number of quality studies in both design categories 1 and 3 were completed to enable meta-analyses of lung function and as-needed short-acting $beta_2$-agonist use outcomes in each category. (See the key evidence tables in this section for a description of eligible studies.) Both the systematic review and meta-analyses confirmed the superiority of combination therapy to inhaled corticosteroids monotherapy. In particular, the findings of the meta-analysis for the addition of long-acting inhaled $beta_2$-agonist compared with increasing the inhaled corticosteroid dosage were consistent with a previously reported meta-analysis (Shrewsbury et al. 2000). In addition to similar findings on lung function, Shrewsbury and colleagues had access to the original data and were able to assess the rate of asthma exacerbations, reporting a positive benefit of the combination

therapy. The data are robust and convincing that the addition of long-acting inhaled beta$_2$-agonists to inhaled corticosteroids improves lung function and asthma control in patients inadequately controlled with low-to-medium doses of inhaled corticosteroids.

Of note is the paucity of pediatric trials in the database. One pediatric study by Verberne et al. (1998) was completed in older children (mean 11 years of age). Following a 6-week run-in, 120 patients were randomized to either low-dose inhaled corticosteroid—beclomethasone dipropionate (BDP) (400 mcg/day), medium-dose BDP (800 mcg/day), or low-dose BDP plus the long-acting inhaled beta$_2$-agonist salmeterol for 1 year. No significant difference was found among any of the three arms in postbronchodilator FEV_1 or PC20 FEV_1 methacholine provocation. These results suggest that the children's asthma was adequately controlled with low-dose inhaled corticosteroids and that the addition of the long-acting inhaled beta$_2$-agonist neither improved nor worsened airway responsiveness. Thus, due to the design, this study cannot refute the potential benefit of the drug combination for those children inadequately controlled on low-dose inhaled corticosteroids alone.

A multicenter double-blind trial of salmeterol as added therapy for children who were not well controlled with inhaled corticosteroids (mean dose of 750 mcg/day) demonstrated significant improvement in morning PEF and symptom-free days in the long-acting inhaled beta$_2$-agonist plus inhaled corticosteroid group, compared to the placebo plus inhaled corticosteroid group (Russell 1995). Although this study did not compare the addition of a long-acting inhaled beta$_2$-agonist to an increased dose of inhaled corticosteroids, the patients were already receiving doses of inhaled corticosteroids ranging from 400 to 2,400 mcg a day. Thus, this study established a need for further asthma control in children already receiving inhaled corticosteroids; it also more directly addresses the question posed by the SRE.

Addition of long-acting oral beta$_2$-agonists

No studies were found.

Addition of cromolyn/nedocromil

No studies meeting the quality criteria of the SRE were found. No new studies since the publication of the EPR-2 were found.

Addition of theophylline

Six studies evaluated the addition of theophylline, including two more recent studies that compared the addition to increased inhaled corticosteroid dosage. The results indicate that the combination of drugs and the increased dose of the inhaled corticosteroids result in equivalent outcomes, suggesting that theophylline has only a modest steroid-sparing effect. None of the four studies (two in children 6 to 19 years of age) comparing the addition of theophylline to a fixed dose of inhaled corticosteroids met the quality criteria of the SRE, because all had study-design and statistical problems. No studies were found that included children younger than 6 years of age.

Addition of leukotriene modifiers

Five published studies evaluated the addition of leukotriene modifiers to fixed doses of inhaled corticosteroids; none compared the combination to increasing the dose of inhaled corticosteroids. Two of these studies used pranlukast, an LTRA unavailable in the United States, and one used zafirlukast in a dose four times the dosage recommended on the package label. None of the studies included children younger than 12 years of age. The most relevant of the five studies (Laviolette et al. 1999), which contributed the most patients and had the longest duration, failed to meet the definition of high quality for the SRE because it met only one of the quality indicators (double blinding). Limitations of these studies preclude definitive conclusions, but they reveal a trend showing improvement in lung function and, in some, symptoms from the combination of leukotriene modifiers and inhaled corticosteroids compared with a fixed dose of inhaled corticosteroids alone.

Addition of an adjunctive agent and down titration of the inhaled corticosteroids

This group of studies is discussed separately, as some of the trials were designed to ask a fundamentally different question (i.e., could the adjunctive therapy ultimately replace inhaled

corticosteroid therapy?). An example is the study that attempted to wean patients from the inhaled corticosteroids after beginning a long-acting inhaled $beta_2$-agonist until they had an exacerbation or the inhaled corticosteroid therapy was discontinued (McIvor et al. 1998). Ten of the 13 patients in the long-acting inhaled $beta_2$-agonist arm experienced an exacerbation only after discontinuing their inhaled corticosteroids, providing further evidence that the long-acting inhaled $beta_2$-agonist should not be used as a substitute for anti-inflammatory therapy. One trial attempted to wean patients from the inhaled corticosteroids after addition of the LTRA montelukast, with the goal of maintaining adequate asthma control (Lofdahl et al. 1999). The mean percentage reduction in the dose of inhaled corticosteroids was 47 percent—a 17 percent increase over placebo—and 40 percent of patients were able to discontinue their inhaled corticosteroids compared with 29 percent in the placebo arm, which was not statistically significant. Thus, data are inconclusive about the "steroid sparing" effect of adjunctive therapy, and data show that patients cannot be entirely weaned from inhaled corticosteroids. In addition, data from these studies are insufficient to determine the relative "steroid-sparing" effect of the various adjunctive therapies. Finally, none of the studies included children younger than 5 years of age.

Additional Literature/Information

In addition to reviewing studies published after the SRE, the Expert Panel considered four other issues relevant to the question of the use of combination therapy for the treatment of persistent asthma: the effect of the different combinations on the rate of exacerbations of asthma; the comparison of different combinations to determine relative effectiveness; the use of combination therapy in children 5 years of age and younger; and the use of combination therapy in severe persistent asthma.

Studies Published After the SRE

The addition of montelukast to inhaled corticosteroids was evaluated in 279 children 6 to 14 years of age with moderate asthma whose symptoms were not completely controlled on 400 mcg budesonide daily (Simons et al. 2001). This study was a double-blinded, randomized, placebo-controlled, crossover trial with a 4-week open-label run-in period to establish the need for adjunctive therapy. Each treatment period also consisted of 4 weeks. The trial had sufficient power (95 percent) to detect a 4.4-percent difference between the placebo and the active drug in the primary end point, FEV_1 percent predicted. In the intention-to-treat analysis, no significant difference was found between the placebo and montelukast for the primary end point (1.3 percent difference). A post hoc censure of the data revealed a statistically significant 1.9 percent difference between the active drug and the placebo. Other significant differences reported in favor of montelukast were a decrease in $beta_2$-agonist usage (.33 puffs/day difference) and exacerbation days that also were defined by $beta_2$-agonist usage—an improvement in morning and evening PEFs (9.7 L/min and 10.7 L/min, respectively). It was not indicated whether these were intention-to-treat analyses. Outcomes found to be the same at the end of the study included worsening asthma, global evaluations, number of asthma attacks requiring intervention, and quality of life.

Another study compared the addition of theophylline to low-dose BDP (400 mcg daily) with increasing the dose of BDP to 1,000 mcg daily or maintaining patients on the low-dose BDP alone for 7 months (Lim et al. 2000). The study found no difference between the high-dose inhaled corticosteroids and the theophylline group for any outcome, thus confirming the SRE findings.

Effect of Combination Therapy on the Rate of Exacerbations of Asthma

Reduction in the rate of asthma exacerbations has been suggested as a surrogate for an anti-inflammatory effect. Compared with placebos, leukotriene modifiers have been reported to reduce the number of exacerbations treated with prednisone (zileuton, zafirlukast, and montelukast package inserts). Both of the long-acting inhaled $beta_2$-agonists—formoterol and salmeterol—have been reported to reduce exacerbations of asthma when administered in conjunction with inhaled corticosteroids (Pauwels et al. 1997; Shrewsbury et al.

2000). In one study, the addition of formoterol to either low-dose (100 mcg bid) or high-dose (400 mcg bid) budesonide significantly reduced both mild and severe exacerbations. Further, fewer exacerbations occurred in the high-dose inhaled corticosteroid group compared with the lower dose group, though statistical analysis was not done (Pauwels et al. 1997). A meta-analysis of studies in which the addition of salmeterol to a lower dose of inhaled corticosteroids was compared with a higher dose of inhaled corticosteroids demonstrated that exacerbations were significantly lower with the combination therapy (Shrewsbury et al. 2000).

It has been suggested that this reduction in exacerbations may be attributed to an enhanced corticosteroid effect due to priming of the glucocorticoid receptor by the long-acting inhaled beta$_2$-agonist (Eickelberg et al. 1999). Two recently published studies (Lazarus et al. 2001; Lemanske et al. 2001) also are pertinent to the issue of using asthma exacerbation as an outcome. In the first trial, those patients adequately controlled on low-dose inhaled corticosteroids were left on the inhaled corticosteroids, switched to the long-acting beta$_2$-agonist salmeterol, or switched to placebo. Although the conventional outcomes (morning and evening PEFs) for the salmeterol and inhaled corticosteroid arms were not different, the salmeterol group had a significantly greater number of exacerbations and treatment failures—again demonstrating that the long-acting inhaled beta$_2$-agonists cannot substitute for inhaled corticosteroids (Lazarus et al. 2001). The companion study evaluated the ability to reduce the dose of inhaled corticosteroids following the introduction of a long-acting inhaled beta$_2$-agonist in those patients initially suboptimally controlled on the inhaled corticosteroids (Lemanske et al. 2001). In this group, the dose of inhaled corticosteroids was reduced by one-half in those patients responding to the addition without any significant change in asthma control, yet a significant treatment failure rate was noted when the inhaled corticosteroids were stopped.

Although clinical studies in the SRE suggest that the addition of a long-acting inhaled beta$_2$-agonist to a low-to-medium dose of inhaled corticosteroids is the most effective treatment for moderate persistent asthma (step 3 care), there may be situations where both the addition of a long-acting inhaled beta$_2$-agonist and an increase in the dose of inhaled corticosteroids are indicated. The studies of Sont et al. (1999) and Pauwels et al. (1997) support the added benefit of a higher dose of inhaled corticosteroids in reducing asthma exacerbations. Thus, for patients considered to be at higher risk for exacerbations (suggested by a history of repeated short courses of prednisone, emergency department visits, or hospitalizations), both the addition of a long-acting inhaled beta$_2$-agonist and an increase in the dose of inhaled corticosteroids may be indicated.

Comparison of Combinations To Determine Relative Effectiveness

Not included in the SRE were direct comparative studies of the effectiveness of the various drugs used as adjuncts to inhaled corticosteroids. Studies comparing the long-acting inhaled beta$_2$-agonist to sustained-release theophylline are numerous (Davies et al. 1998), and generally involve patients receiving inhaled corticosteroids. A meta-analysis of these studies (Davies et al. 1998) demonstrated that both pulmonary function and asthma symptoms showed more improvement with the long-acting inhaled beta$_2$-agonist as adjunctive therapy than with theophylline. In the three published studies included in the meta-analysis, between 50 percent and 97 percent of the subjects were receiving regular inhaled corticosteroid therapy (Fjellbirkeland et al. 1994; Muir et al. 1992; Paggiaro et al. 1996).

A comparison of the addition of the long-acting beta$_2$-agonist salmeterol to the addition of the LTRA zafirlukast (Busse et al. 1999) also examined a mixed population; however, this study was not included in the SRE because more than 80 percent of the patients in both arms were using inhaled corticosteroids, rather than 90 percent required by the SRE selection criteria. The study otherwise met the criteria for a high-quality study and should be considered. The results indicate that salmeterol improved both pulmonary function and asthma symptoms significantly more than did zafirlukast.

Another direct comparison of long-acting inhaled $beta_2$-agonists and a leukotriene modifier as combination therapy was published after the SRE (Nelson et al. 2000). This study also met the SRE criteria for high quality and should be considered. The investigators evaluated patients who were still symptomatic on low-dose inhaled corticosteroids (fluticasone 88 mcg bid), before and after the addition of the long-acting $beta_2$-agonist salmeterol or the LTRA montelukast over 3 months. Those patients receiving salmeterol plus fluticasone, compared with those on montelukast and fluticasone, had greater improvement in pulmonary function and in some asthma symptoms, and experienced significantly fewer exacerbations.

Although the addition of sustained-release theophylline or a leukotriene modifier to treatment with inhaled corticosteroids generally is not as effective as the addition of a long-acting inhaled $beta_2$-agonist, there may be circumstances when these combinations would be indicated for selected patients. Among the considerations favoring one of these alternative combinations would be the patient's intolerance of the side effects of the long-acting inhaled $beta_2$-agonist, marked preference for oral therapy, demonstration of superior responsiveness to the alternate class of drug, as well as financial considerations (theophylline is the least expensive). Finally, although the recently marketed fixed-dose combination of fluticasone propionate and salmeterol in a DPI may provide an advantage in terms of ease of use (one inhaler instead of two), there is no evidence of superiority of this particular combination over that of other inhaled corticosteroids and long-acting inhaled $beta_2$-agonists.

Combination Therapy in Children 5 Years of Age and Younger

None of the adjunctive therapy combinations have been adequately studied in children 5 years of age and younger. Indeed, only one study, a study adding the long-acting inhaled $beta_2$-agonist salmeterol to inhaled corticosteroids, included patients as young as 4 years of age (Russell 1995). The lower age limit of all other combination therapy studies in children is 6 years of age (Simons et al. 2001; Meltzer et al. 1992; Nassif et al. 1981). The data are thus inadequate to provide definitive recommendations on combination therapy in young children, and recommendations must be extrapolated from studies in older children and adults, which support the combination of inhaled corticosteroids and long-acting inhaled $beta_2$-agonists. Because patients in this age range may be at greater risk for systemic effects from high doses of inhaled corticosteroids, the use of combination therapy seems prudent when goals of therapy are not attained with low or the lower range of medium doses of inhaled corticosteroids. However, as noted in the section on effectiveness of long-term-control medications, there are no data available on the use of long-acting inhaled $beta_2$-agonists in infants and young children, whereas studies of medium doses of inhaled corticosteroids demonstrate effectiveness in this age group.

The following medications have been FDA-approved for young children: the inhaled corticosteroids budesonide nebulizer solution approved for children 1 to 8 years of age and fluticasone DPI approved for children 4 years of age and older; the long-acting inhaled $beta_2$-agonist salmeterol DPI approved for children 4 years of age and older; and, based on safety data rather than efficacy data, the LTRA montelukast 4 mg chewable approved for children 2 to 6 years of age.

Combination Therapy in Patients With Severe Persistent Asthma

Current recommendations for treatment include adding oral systemic corticosteroids if a patient cannot achieve and maintain control with high doses of inhaled corticosteroids and long-acting bronchodilators. An alternative approach may be to add a third long-term-control medication to a combination of medium-to-high-dose corticosteroids and long-acting inhaled $beta_2$-agonists in severe persistent asthma. However, few trials regarding this approach and of sufficient quality are available. A double-blind, crossover trial of LTRA (10 mg montelukast or placebo) in 72 adults with severe persistent asthma found no benefit from the addition of montelukast to other medication (Robinson et al. 2001). In this study, the concurrent medication varied among the patients: All patients received medium-to-high-dose inhaled

corticosteroids; 85 percent also received either theophylline, a long-acting inhaled beta$_2$-agonist, or both; and 47 percent also received oral systemic corticosteroids. No attempt was made to eliminate the oral corticosteroids. The treatment period of 14 days for LTRA and 14 days for placebo was relatively short, although leukotriene modifiers usually produce a rapid response. This study indicates that there is no additional benefit to adding LTRA as a third medication. Similar controlled clinical trials have not been conducted to evaluate other long-term-control medications added to the combination of medium-to-high doses of inhaled corticosteroids and long-acting inhaled beta$_2$-agonists in severe persistent asthma. Until more research is conducted, recommendations for managing severe persistent asthma are based on extrapolations from studies of the combination of inhaled corticosteroids and one other long-term-control medication in treating moderate persistent asthma.

Recommendations for EPR-2 Update

Based upon the assessment of evidence provided by the SRE and the additional evidence considered by the Expert Panel, the following changes to step 3 care in EPR-2 are recommended:

- The preferred treatment for those adults and children older than 5 years of age whose asthma is inadequately controlled on low-dose inhaled corticosteroids is combination therapy: the addition of a long-acting inhaled beta$_2$-agonist (SRE-Evidence A) to a low-to-medium dose of inhaled corticosteroids. Scientific evidence from studies of children older than 12 years of age and adults indicates that patients with moderate persistent asthma benefit from two different types of daily medication in order to achieve and maintain optimal control of their asthma: (1) medication aimed at suppressing underlying airway inflammation and (2) a medication whose primary action is bronchodilation. This approach is preferred to increasing the dose of inhaled corticosteroids.

  The exception is indicated for those patients who experience recurring severe exacerbations that require oral prednisone, emergency department visits, or hospitalizations. For these patients, increasing the dose of inhaled corticosteroids along with the addition of a long-acting inhaled beta$_2$-agonist should be considered (SRE-Evidence B).

  For children 5 years of age or younger, combination therapy has not been adequately studied. Therefore, recommendations for step 3 care for this age group are based on extrapolations of data from older children and adults, as well as expert opinion. For children 5 years of age and younger with moderate persistent asthma, there are two equally preferred options: low-dose inhaled corticosteroids and a long-acting beta$_2$-agonist (Evidence B, extrapolation from studies in older children and adults) OR inhaled corticosteroids as monotherapy with an increase of the dose within the medium-dose range (Evidence D).

  - Alternative—but not preferred—approaches that may be considered include doubling the dose of inhaled corticosteroids within the medium-dose range (this is an alternative but not preferred option for older children and adults; for children 5 years of age and younger, increasing the inhaled corticosteroid dose is an equally preferred option); adding sustained-release theophylline; or adding a leukotriene modifier (SRE-Evidence B). Leukotriene modifiers or theophylline may be considered if the patient displays intolerance of long-acting inhaled beta$_2$-agonists, has a marked preference for oral therapy, and demonstrates superior responsiveness to the alternative class of drug through a therapeutic trial. Other issues may include financial considerations (theophylline is the least expensive).

- The recommendations for the use of nedocromil and long-acting oral beta$_2$-agonists as alternatives to increasing the dose of inhaled corticosteroids are untenable at this time due to lack of data and should be removed as therapeutic options.

Specifically, the Expert Panel recommends that step 3 in figure 3–4b, Stepwise Approach for Managing Asthma in Adults and Children Older Than 5 Years of Age, be revised as follows with the revision noted in blue text.

Figure 3–6. Stepwise Approach for Managing Infants and Young Children (5 Years of Age and Younger) With Acute or Chronic Asthma. (See Medications: Effectiveness in Children on page 25 of this report for revisions to step 3.)

Figure 3–4b. Stepwise Approach for Managing Asthma in Adults and Children Older Than 5 Years of Age: Treatment (pages 84 through 85 in EPR-2)

Step 3: Moderate Persistent
Daily Medications:
Preferred treatment:
  Low-to-medium-dose inhaled corticosteroids and long-acting inhaled $beta_2$-agonists
Alternative treatment (listed alphabetically):
  Increase inhaled corticosteroids within medium-dose range
  OR
  Low-to-medium-dose inhaled corticosteroids and either a leukotriene modifier OR theophylline

If needed (particularly in patients with recurring severe exacerbations)
Preferred treatment:
  Increase inhaled corticosteroids within medium-dose range and add a long-acting $beta_2$-agonist
Alternative treatment:
  Increase inhaled corticosteroids within medium-dose range and add either a leukotriene modifier
  OR
  Theophylline

Step 4: Severe Persistent
Daily Medication:
Preferred treatment:
  High-dose inhaled corticosteroids

  AND

  Long-acting inhaled $beta_2$-agonists

  AND, if needed

  Corticosteroid tablets or syrup long term (1 to 2 mg/kg/day; generally do not exceed 60 mg/day). (Make repeat attempts to reduce systemic corticosteroids and maintain control with high-dose inhaled corticosteroids.)

The text in EPR-2 on pages 93 and 94 regarding step 3 and step 4 care for adults and children older than 5 years of age should be revised as follows, with the blue text indicating new text. (See Medications: Effectiveness in Children on page 25 for revisions to step 3 for children 5 years of age and younger.)

Step 3: Moderate Persistent Asthma
Consultation with an asthma specialist may be considered because the therapeutic options at this juncture pose a number of challenging risk-benefit outcomes. Before increasing therapy, however, the clinician should review the patient's inhaler technique and adherence, as well as determine whether environmental factors are contributing to the patient's worsening asthma. If a step-up in therapy is required, there are at least four options for initiating step 3 therapy.

Add a long-acting inhaled $beta_2$-agonist to a low-to-medium-dose of inhaled corticosteroids (SRE-Evidence B). This is the preferred treatment. Early investigations suggested that the addition of a long-acting inhaled $beta_2$-agonist to a low (Greening et al. 1994) or medium (Woolcock et al. 1996) dose of inhaled corticosteroids resulted in greater improvement in lung function and overall asthma control than doubling the dose of inhaled corticosteroids. Since that time, numerous studies have confirmed the superiority of combination therapy over increasing the dose of inhaled corticosteroids, even for reducing severe asthma exacerbations (SRE 2002; Shrewsbury et al. 2000). The use of combination therapy has not been shown to mask worsening of inflammation and asthma. Indeed, the combination has consistently been shown to reduce the number of severe asthma exacerbations (Pauwels et al. 1997; Shrewsbury et al. 2000). This approach has proved so successful that it has spawned the development of two fixed-dose combinations of long-acting inhaled $beta_2$-agonists and inhaled corticosteroids in one inhaler, one currently marketed. The fixed-dose combination may be easier to use and hence facilitate adherence to the regimen, but there is no evidence of clinical superiority over using the inhaled corticosteroids and long-acting inhaled $beta_2$-agonists in separate inhalers.

OR

- Increase the dose of inhaled corticosteroids *and* add a long-acting inhaled $beta_2$-agonist (SRE-Evidence B). This approach should be reserved for those patients experiencing recurring severe exacerbations [illegible] prednisone, emergency [illegible] hospitalizations. In a [illegible] therapy, the addition [illegible] $beta_2$-agonists to either low-dose [illegible] inhaled corticosteroids signific[illegible]duced [illegible]ild and severe exacer[illegible]Pau[illegible]997). In addition, fewer [illegible] the high[illegible]dose inhaled [illegible]roid group compared with [illegible]lower-dose group, although analysis [illegible] not done.

OR

- Give inhaled corticosteroids a[illegible]py by increasing the dose within the [illegible]ose range (SRE-Evidence A, B). This approach [illegible] another preferred treatment option for [illegible] children; it is an alternative, but not preferred, treatment option for older children and adults. Studies of adults in which the dose of inhaled corticosteroids was at least doubled consistently demonstrate improved lung function and other outcomes in those patients not completely controlled on low-to-medium-doses of inhaled corticosteroids, but these results are consistently less effective than adding a long-acting inhaled $beta_2$-agonist (SRE-Evidence A, B).

OR

- Add a leukotriene modifier or theophylline to inhaled corticosteroids (SRE-Evidence B; Evidence B). The addition of leukotriene modifiers and theophylline has produced modest improvement in lung function and some other outcomes in patients not completely controlled on inhaled corticosteroids. The addition of theophylline, however, has not been shown to be more effective than doubling the dose of inhaled corticosteroids (Evans et al. 1997; Ukena et al. 1997). The leukotriene modifiers have produced improvements in lung function and in some but not all measures of asthma control in patients incompletely controlled on inhaled corticosteroids (Laviolette et al. 1999). In addition, the leukotriene modifiers allow slightly more patients to be taken off inhaled corticosteroids than does placebo (11 percent difference) (Lofdahl et al. 1999). The addition of the leukotriene modifiers to inhaled corticosteroids has not been compared with doubling the dose of inhaled corticosteroids. Direct comparisons of the addition of a leukotriene modifier or a long-acting inhaled $beta_2$-agonist to therapy for patients incompletely controlled on inhaled corticosteroids show significantly greater improvement in lung function and other measures of asthma control for patients receiving the long-acting inhaled $beta_2$-agonist and inhaled corticosteroid combination (Busse et al. 1999; Nelson et al. 2000). Thus, although the combination of inhaled corticosteroids and either theophylline or leukotriene modifier is not the [illegible]ed approach, considerations favoring one [illegible]ese alternative combinations would be the [illegible]atient's intolerance of the side effects of the long-[illegible] inhaled $beta_2$-agonist, marked preference [illegible] therapy [illegible]nd demonstration of superior [illegible]nsiveness [illegible]e alternative class of drug, [illegible]as well [illegible]ical considerations (theophylline [illegible]is [illegible]xpensive).

[illegible]ssues [illegible]l. Recommendations on [illegible]mbinati[illegible]apy [illegible] children younger than 12 years [illegible]e w[illegible]ate persistent asthma are b[illegible]ions from studies in older c[illegible]nd ad[illegible]n expert opinion (Evidence B, D). N[illegible]ive therapy [illegible]mbinations hav[illegible]uate[illegible]died in children younger th[illegible]years [illegible]d they have not be[illegible]st[illegible]died at al[illegible]hi[illegible]ren [illegible]ger than 4 years of [illegible]e negative [illegible]combination therapy in chil[illegible]th mild or moderate persistent asthma failed to [illegible]sh a need in the study participants at baseline [illegible]more therapy than low-dose inhaled corticosteroids and thus did not sufficiently address the question of combination therapy (Verberne et al. 1998). In one study in children 4 to 16 years of age with moderate or severe asthma, the addition of a long-acting $beta_2$-agonist produced a clear benefit compared to placebo (Russell et al. 1995). In a recent crossover comparison of children 6 to 14 years of age on inhaled corticosteroids, no significant difference was found with the addition of the LTRA montelukast in the primary outcome measure FEV_1, but a small reduction in as-needed short-acting

beta$_2$-agonist use (.33 puffs/day) in favor of LTRA was found. No difference was found for worsening asthma, asthma attacks, or quality of life (Simons et al. 2001). Studies of the addition of theophylline to inhaled corticosteroids in children [illegible] years of age showed both a benefit [illegible] and no benefit (Melt[illegible]). Ne[illegible] these theophylline stu[illegible] er[illegible]uality to generat[illegible] recomm[illegible]dati[illegible] here is only one [illegible]on adjunctive th[illegible] inc[illegible] hildren a[illegible] as 4 years [illegible] studies i[illegible] children younge[illegible]

Step 4: Severe Persistent Asthma

Patients with se[illegible] persistent asthma [illegible] high doses of inha[illegible] orticosteroids [illegible] ong-acting inhaled beta$_2$-[illegible]gonist and, if n[illegible], an oral corticosteroid (Evi[illegible] B). It is [illegible] opinion of the Expert Pa[illegible] hat consult[illegible] with an asthma specialist is recommended for patients with severe persister[illegible] sthma. Evide[illegible] to date does not support using a thi[illegible] long-term-control medication added to inhaled cor[illegible]steroids and long-acting inhaled beta$_2$-agonists in order to avoid using systemic corticosteroid therap[illegible] (Evidence C). A study found no benefit for th[illegible] addition of an LTRA to high doses of inhaled corticosteroids and, for most patients in the study, another medication (either theophylline, a long-acting beta$_2$-agonist, oral corticosteroid, or a combination) (Robinson et al. 2001). Similar studies of other long-term-control medications added to the combination of medium-to-high doses of inhaled corticosteroids and long-acting inhaled beta$_2$-agonists in severe persistent asthma are not available.

Patients whose asthma is not controlled on high doses of inhaled corticosteroids and the addition of long-acting inhaled beta$_2$-agonists also will need oral systemic corticosteroids on a regularly scheduled, long-term basis. For patients who require long-term systemic corticosteroids:

- Use the lowest possible dose (single dose daily or, preferably, on alternate days).
- Monitor patients closely for corticosteroid adverse side effects (see component 3-Medications).
- When control of asthma is achieved, make persistent attempts to reduce systemic corticosteroids. High doses of inhaled corticosteroids are preferable to systemic corticosteroids because inhaled corticosteroids have fewer systemic effects.
- Recommend consultation with an asthma specialist.

Recommendations for Future Research

The Panel recommends the following research to clarify treatment options:

- Long-term studies to examine the effect of adjunctive therapy on possible loss in pulmonary function and the natural history of asthma—hospitalization, exacerbations, and decline in pulmonary function.
- Studies of noninvasive markers that would give a composite picture of both disease activity (e.g., inflammation) and disease control. These could be used as surrogate markers for overall asthma control to guide therapy. Ideally, such markers would be more efficient than gauging a patient's response to therapy following a relatively long therapeutic trial.
- Long-term studies to examine the importance of the greater suppression of inflammation achievable with higher doses of inhaled corticosteroids compared with adjunctive therapy. Low doses of inhaled corticosteroids usually are sufficient for improvement in lung function and control of asthma symptoms but may not suppress inflammation to the same extent as higher doses. Studies to assess the value of maximum suppression of inflammation vis-à-vis therapeutic control will contribute to understanding the appropriate use of inhaled corticosteroids and adjunctive therapy.
- Evaluations of adjunctive therapies in children younger than 12 years of age.

Key Evidence Tables

Table 1-6. Meta-Analysis: Lung Function Outcomes for Studies Comparing the Addition of Long-Acting Beta$_2$-Agonists to a Fixed Dose of Inhaled Corticosteroids

Meta-Analysis	Effect Size Estimate	95% CI	Test for Homogeneity P-Value	Treatment Effect Estimate	95% CI
FEV_1: Combined Studies (n = 14)	0.334	0.241, 0.428	0.10	0.17 L 3.71% pred	0.12, 0.22 2.67, 4.75
FEV_1: Sensitivity analysis by quality: Studies that meet all generic quality criteria except allocation concealment and meet most (>4) asthma-specific criteria (n = 3)	0.319	0.139, 0.499	0.14	0.17 L 3.43% pred	0.07, 0.26 1.54, 5.54
FEV_1: Sensitivity analysis by quality: Studies that meet all generic quality criteria except allocation concealment (N = 11)	0.368	0.257, 0.478	0.20	0.19 L 4.08% pred	0.13, 0.25 2.85, 5.30
PEF: Combined studies (n = 9)	0.581	0.417, 0.745	0.0034	24.68 L/min 7.26% pred	17.70, 31.65 5.21, 9.31
PEF: Sensitivity analysis by quality: Studies that meet all generic quality criteria except allocation concealment and meet most (>4) asthma-specific criteria (n = 4)	0.643	0.460, 0.826	0.17	27.33 L/min 8.04% pred	19.55, 35.10 5.75, 10.32
PEF: Sensitivity analysis by quality: Studies that meet all generic quality criteria except allocation concealment (n = 8)	0.630	0.478, 0.781	0.06	26.77 L/min 7.88% pred	20.32, 33.19 5.98, 9.76

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44. AHRQ Publication No. 01-E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Table 1-7. Meta-Analysis: Medication Use Outcomes for Studies Comparing the Addition of Long-Acting Beta$_2$-Agonists to a Fixed Dose of Inhaled Corticosteroids

Meta-Analysis	Treatment Effect Estimate	95% CI	Test for Homogeneity P-Value
Puffs/day: Combined studies (n = 6)	-1.18	-1.56, -0.80	0.018
Puffs/day: Sensitivity analysis by quality: Studies that meet all generic quality criteria except allocation concealment and meet most (>4) asthma-specific criteria (n = 3)	-1.34	-1.87, -0.84	0.20
Puffs/day: Sensitivity analysis by quality: Studies meet all generic quality criteria except allocation concealment (n = 5)	-1.00	-1.34, -0.66	0.14

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44. AHRQ Publication No. 01-E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Table 1–8. Meta-Analysis: Lung Function Outcomes for Studies Comparing a Lower Dose of Inhaled Corticosteroids Plus Long-Acting Inhaled Beta$_2$-Agonist to Increased Dose of Inhaled Corticosteroids

Meta-Analysis	Effect Size Estimate	95% CI	Test for Homogeneity P-Value	Treatment Effect Estimate	95% CI
FEV_1: Combined Studies (n = 8)	0.209	0.133, 0.285	0.93	0.11 L 2.32% pred	0.07, 0.15 1.48-3.16
FEV_1: Sensitivity analysis by quality: Studies that that meet all generic quality criteria except allocation concealment and meet most (>4) asthma-specific criteria (n = 4)	0.203	0.107, 0.299	0.94	0.11 L 2.25% pred	0.06, 0.16 1.19, 3.32
FEV_1: Sensitivity analysis by quality: Studies that meet all generic quality criteria except allocation concealment (n = 7)	0.212	0.134, 0.290	0.88	0.11 L 2.35% pred	0.07, 0.15 1.49, 3.22
PEF: Combined studies (n = 10)	0.310	0.192, 0.429	0.0002	11.6 L/min 3.4% pred	5.2-18.0 1.5-5.3
PEF: Sensitivity analysis by quality: Studies that meet all generic quality criteria except allocation concealment and meet most (>4) asthma-specific criteria (n = 4)	0.300	0.030, 0.569	0.000007	12.75 L/min 3.75% pred	1.28, 24.18 0.38, 7.11
PEF: Sensitivity analysis by quality: Studies that meet all generic quality criteria except allocation concealment (n = 7)	0.296	0.143, 0.449	0.00005	12.58 L/min 3.7% pred	6.08, 19.08 1.79, 5.61

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44. AHRQ Publication No. 01–E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

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Use of Antibiotics To Treat Asthma Exacerbations

Question

Does routinely adding antibiotics to standard care improve the outcomes of treatment for acute exacerbation of asthma? Does the addition of antibiotics to standard care in the following populations improve the outcomes of treatment for an acute exacerbation of asthma: patients without signs and symptoms of bacterial infection; patients with signs and symptoms of a bacterial infection; patients with signs and symptoms of sinusitis?

Summary Answer to the Question

The available evidence (two randomized, controlled clinical trials) suggests no benefit from antibiotic therapy for asthma exacerbations, whether administered routinely or when suspicion of bacterial infection is low (SRE-Evidence B). No studies addressed the question of greatest relevance to contemporary clinical practice: whether the addition of antibiotics to standard care when signs and symptoms suggest the possibility—but do not clearly indicate the presence—of bacterial infection improves the outcomes of treatment for acute asthma exacerbations.

The EPR-2 recommendation has not been changed: Antibiotics are not recommended for the treatment of acute asthma exacerbations except as needed for comorbid conditions—e.g., for the patients with fever and purulent sputum, evidence of pneumonia, or suspected bacterial sinusitis.

Rationale for the Question

Asthma exacerbations often are associated with clinical signs of infection, such as purulence of expectorated sputum or nasal discharge. Most asthma exacerbations are associated with infection by a respiratory virus, especially rhinovirus (Nicholson et al. 1993; Johnston et al. 1995), but a small percentage of exacerbations are associated with infection by an atypical bacterium, like Mycoplasma pneumoniae or Chlamydia pneumoniae (Freymuth et al. 1999). It is widely believed that coincident bacterial sinusitis contributes to asthma exacerbations, and some clinicians have postulated that airway obstruction due to mucus plugging—common in asthma—predisposes patients to bacterial infection of nondraining regions of the lungs.

In the absence of clear signs of bacterial infection (e.g., lobar pulmonary infiltrate on chest radiography distinguishing viral from bacterial infections), infection is often difficult to manage. Viral infections commonly resemble bacterial infections in that they also cause neutrophilic inflammation of the upper and lower airways (Teran et al. 1997; Trigg et al. 1996; Fahy et al. 1995). This difficulty, coupled even with the remote possibility that bacterial infection may be associated with an asthma exacerbation, may account for the frequency with which antibiotics are prescribed in addition to inhaled bronchodilators, inhaled or systemic corticosteroids, and supplemental oxygen.

Systematic Review of the Evidence

The following description of the SRE is an adaptation of the evidence report, including direct excerpts, submitted by the Blue Cross Blue Shield Association Evidence-Based Practice Center. (See Introduction, Methods.)

Methods of Literature Search

In addition to the selection criteria for studies related to all topics in the SRE (described in the Introduction section), studies for this question were included in which standard care (asthma medications) plus antibiotics was compared with standard care alone in the treatment of acute asthma exacerbations. Patient populations included patients without signs and symptoms of bacterial infection, patients with signs and symptoms of bacterial infection, and patients with signs and symptoms of sinusitis.

Summary of Findings

Studies

Only two randomized, double-blind, placebo-controlled, parallel-group trials—with a total enrollment of 121 patients—have addressed the question of whether routinely adding antibiotics to standard care improves the outcomes of treatment for acute asthma exacerbations (Shapiro et al. 1974; Graham et al. 1982). (See the key evidence tables in this section.) Both trials studied patients hospitalized for asthma exacerbations. Both used a penicillin derivative whose activity against atypical bacteria was unknown. Shapiro and colleagues examined the effects of hetacillin (an analogue of ampicillin; 100 mg/kg every 24 hours for a minimum of 24 hours, then 225 mg four times per day for 6 days) in 50 children who did not exhibit clinical evidence of bacterial infection. Graham and colleagues examined the effects of amoxicillin (500 mg three times per day) in 60 adults and adolescents who experienced a total of 71 hospital admissions. Whereas the pediatric study explicitly excluded patients with clinical evidence of bacterial infection, the study of adults and adolescents excluded only patients with evidence of pneumonia on chest radiography. Thus, the populations in these studies consisted primarily of patients without signs or symptoms of bacterial illness, including suspected acute sinusitis.

In both trials, all patients received standard care that included high-dose oral or intravenous corticosteroids and regularly scheduled $beta_2$-agonist treatment. In the pediatric study, all patients were also treated with intravenous aminophylline followed by oral theophylline.

The study design and conduct for these two trials did not meet the SRE criteria for higher quality because of deficiencies in allocation concealment, subject withdrawal, and reporting of power calculations.

The outcomes analyzed included change in FEV_1, symptom scores, and length of hospital stay.

Results of Studies

Neither study reported an association—nor a trend towards an association—between antibiotic treatment and greater improvement in any asthma outcome. Therefore, available evidence suggests no benefit from the use of antibiotic treatment for asthma exacerbations either routinely or when the suspicion of bacterial infection is minimal. (See key evidence tables 1–11 and 1–12.)

Additional Literature/Information

A related question, for which clinical trials data are unavailable, should ask whether the use of an antibiotic active against Mycoplasma and Chlamydia would alter outcomes. Some recent studies using polymerase chain reaction (PCR)-based methods for detecting specific genomic sequences have suggested that chronic infection with these organisms may contribute to the severity of chronic asthma (Kraft et al. 1998). These highly sensitive methods have not yet been applied to the analysis of airway tissue or secretions obtained from patients suffering acute exacerbations. Thus, there is a theoretical basis for the concept that a subgroup of patients with asthma exacerbations may benefit from treatment with an antibiotic that is active against these atypical bacteria.

The EPR-2 statement that "the use of antibiotics is generally reserved for patients with fever and purulent sputum (discolored because of polymorphonuclear leukocytes, not eosinophils)" comes under scrutiny because low-grade fever also may accompany viral respiratory infections. Furthermore, a recent study shows that discoloration of sputum by polymorphonuclear leukocytes is observed in viral tracheobronchitis, and the sputum from patients suffering from uncomplicated asthma exacerbations commonly contains high numbers of polymorphonuclear leukocytes (Fahy et al. 1995).

Recommendations for EPR Update

No evidence supports changing the EPR-2 recommendation (SRE-Evidence B). The parenthetical statement on page 116 of EPR-2 ["(discolored because of polymorphonuclear leukocytes, not eosinophils)"] should be removed (Evidence C). The recommendation can otherwise stand and is as follows:

Antibiotics are *not* recommended for the treatment of acute asthma exacerbations except as needed for comorbid conditions. Bacterial, *Chlamydia*, or *Mycoplasma* infections infrequently contribute to exacerbations of asthma and therefore the use of antibiotics is generally reserved for patients with fever and purulent sputum and for patients with evidence of pneumonia. When the presence of bacterial sinusitis is suspected, treat with antibiotics.

Recommendations for Future Research

No studies addressed the question of greatest relevance to contemporary clinical practice—whether the addition of antibiotics to standard care when signs and symptoms suggest the possibility but do not clearly indicate the presence of bacterial infection improves the outcomes of treatment for acute asthma exacerbations. The two trials reviewed excluded the patients most likely to be treated with antibiotics and those with signs or symptoms suggestive of bacterial infection, including suspected acute sinusitis. Studies of the efficacy of antibiotic treatment in this group are needed.

Several studies are needed to clarify the role of antibiotics in the treatment of asthma exacerbations. Questions for research are as follows:

- What is the efficacy of antibiotic treatment in asthma patients most likely to be treated with antibiotics, such as those with signs suggestive of bacterial infection, including suspected acute sinusitis? The role of sinusitis in acute exacerbations of asthma has not been truly defined.

- What is the role of sinusitis in acute exacerbations of asthma or increased asthma severity?

- What is the efficacy of using an antibiotic active against atypical bacteria, given the possibility that such bacteria commonly contribute to asthma exacerbations?

- What would be the value of studies applying modern sensitive methods of detection of atypical bacteria (e.g., PCR-based methods) to samples of airway tissues or secretions obtained at the time of an asthma exacerbation?

  Do antibiotics such as macrolides have a non-antibiotic action (e.g., anti-inflammatory) that is beneficial in asthma patients?

Key Evidence Tables

Table 1-9. Study Characteristics

Citation	Study Design	Study Setting	Asthma Severity	Eligibility
Graham, Milton, Knowles et al. 1982	Randomized, double-blind, placebo-controlled, parallel group trial	Country: United Kingdom Funding: Government grant Tx setting: University Hospital, inpatient setting	Stated: Not specified Estimated: Unable to estimate	Eligibility assessed on admission to hospital with asthma exacerbation: • FEV_1 of 1.5L or less and/or PEF of 150 l/min • Reversibility of FEV_1 at least 15% spontaneously or after inhalation of $beta_2$-agonist Exclusions: Evidence of pneumonia on CXR, history of penicillin allergy
Shapiro, Eggleston, Pierson et al. 1974	Randomized, double-blind, placebo-controlled, parallel group trial	Country: United States Funding: Pharm Industry and Government grant Tx setting: Hospital, inpatient setting	Stated: Not specified Estimated: Unable to estimate	Eligibility assessed on admission to hospital with asthma exacerbation: • Severe bronchospasm, lack of response to subcutaneous epinephrine Exclusions: Clinical evidence of bacterial infection; recent use of antibiotics

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence* **Report/T**echnology Assessment Number 44. AHRQ Publication No. 01–E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Table 1–10. Study Parameters

Citation	Study Arm	Treatment	Comments
Graham, Milton, Knowles et al. 1982	Placebo	Placebo tablet 3 times per day Oral prednisolone (20–60 mg/day) and/or IV hydrocortisone (100–200 mg every 4 to 6 hours) Regularly scheduled $beta_2$-agonists and/or phosphodiesterase inhibitors Chest physiotherapy	60 patients enrolled with 71 exacerbations. Unit of analysis by exacerbations.
	Antibiotics	Amoxicillin 500 mg 3 times per day Oral prednisolone (20–60 mg/day) and/or IV hydrocortisone (100–200 mg every 4 to 6 hours) Regularly scheduled $beta_2$-agonists and/or phosphodiesterase inhibitors Chest physiotherapy	Culture-proven bacterial source of infection found in two patients on admission and two patients on discharge
Shapiro, Eggleston, Pierson et al. 1974	Placebo	Placebo 4 times per day for 6 days IV hydrocortisone (7 mg/kg/24 hr) for 24 hours, followed by oral prednisone IV aminophylline (15 mg/kg/24 hr) for 24 hours, followed by oral theophylline Nebulized $beta_2$-agonists q30 min x 4, then as needed	37 patients enrolled with 44 exacerbations, unit of analysis by exacerbation
	Antibiotics	Hetacillin (100 mg/kg/24 hr) for at least 24 hours, followed by oral hetacillin 225 mg 4 times per day for 6 days IV hydrocortisone (7 mg/kg/24 hr) for 24 hours, followed by oral prednisone IV aminophylline (15 mg/kg/24 hr) for 24 hours, followed by oral theophylline Nebulized $beta_2$-agonists q30 min x 4, then as needed	

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01–E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Key Evidence Tables

Table 1-11. Lung Function Outcome

Citation	Study Arm	Number Enrolled	Number Evaluable	Study Duration (days) (median/range)	FEV_1 Baseline (mean)	
Graham, Milton, Knowles et al. 1982	Placebo	71*	32*	8 (3–16)	20.9 (<7.3–63)	
	Antibiotics	71*	37*	7 (3–25)	23.1 (<7.3–45.5)	
Shapiro, Eggleston, Pierson et al.1974	Placebo	50*	24*	2.9 (SD 1.4)	26.5 (SD 15)	
	Antibiotics	50*	20*	2.5 (SD 0.8)	28.3 (SD 11)	

Table 1-12. Symptoms/Utilization Outcome

Citation	Study Arm	Number Enrolled	Number Evaluable	Study Duration (days) (median/range)	
Graham, Milton, Knowles et al. 1982	Placebo	34	32	8 (3–16)	
	Antibiotics	37	37	7 (3–25)	
Shapiro, Eggleston, Pierson et al. 1974	Placebo	24	24	2.9 (SD 1.4)	
	Antibiotics	20	20	2.5 (SD 0.8)	

	FEV_1 Final (mean)	...lue	PEF Baseline (mean/range)	PEF Final (mean/range)	P-Value
	65.6 (31.5–108.5)		23.8 (<9.4–83.9)	72.8 (32.8–108.1)	
	52.3 (10–92.9)	0.039	23.8 (<9.4–47.3)	59 (16.7–95)	0.052
	49 (SD 17)		NR	NR	
	61 (SD 19)	NR	NR	NR	

*Unit of analysis was admission. Number enrolled represented total admissions in both groups, information not provided by group. Number evaluated represents total number of admissions included in analysis.

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01-E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

	Baseline Symptom Score (median/range)	Final Sym...Score (median/rang...	P-Value	...spital ...th of Stay	P-Value
	11 (6–12)	4 (4–8)		8 (3–16)	
	11 (5–12)	5 (4–9)	NS	7 (3–25)	NS
	7.1 (mean) (SD 2.2)	2.5 (SD 2.0)		2.9 (SD 1.4)	
	7.1 (mean) (SD 1.8)	2.0 (SD 2.0)	NR	2.4 (SD 0.8)	

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01-E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

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Expert Panel Report
Guidelines for the
Diagnosis and
Management of
Asthma

2 Monitoring

2. Monitoring

Two distinct questions have been raised regarding the use of written action plans in the management of asthma. First, does the use of written action plans make a difference in patient outcomes beyond those accomplished by appropriate medical/pharmacologic management? Second, is there a difference in patient outcomes between action plans based on symptom monitoring and those based on peak flow monitoring? This section of the EPR Update considers both questions.

Written Ac... ...pared to Medica... ...geme... ...lone

Question

Compared to medical management alone, does the use of a written asthma action plan improve outcomes?

Summary A... ...er to the Quest...

Data are insufficient to support or refute the benefits of using written asthma action plans compared to medical management alone (SRE-Evidence B). Seven studies compared medical management with written action plans to medical management without action plans. Beyond including instructions on the action plan to the intervention groups, four of these studies did not include asthma education for either the intervention or control groups; three of the studies included similar but limited asthma education for both intervention and control groups. Only one study included children. Significant limitations in study designs and methods in these studies preclude conclusions. For example, the studies showing no benefits of written action plans did not have sufficient power for comparisons between treatment and control groups, and the two studies reporting significant improvements with action plans had potential biases in patient selection, withdrawals, data collection, or analysis.

However, a Cochrane review of 25 studies comparing asthma self-management education interventions for adults to medical care without such education also contrasted those studies with self-management interventions that included written action plans to those that did not. The self-management interventions that included written action plans had the greatest benefits, including reduced emergency department visits and hospitalizations and improved lung function.

The EPR-2 recommendations have not been changed: It is the opinion of the Expert Panel that use of written action plans as part of an overall effort to educate patients in self-management is recommended, especially for patients with moderate or severe persistent asthma and patients with a history of severe exacerbations (Evidence B, C).

...on... ...e Question

The use of written action plans is recommended in the EPR-2 and is widely accepted as good practice. Generally, the use of written action plans has been studied as part of self-management education (Gibson et al. 2000). In busy practices, however, physicians often provide their patients with action plans independent of other asthma education efforts. This question was posed in order to identify data that describe the effects of using written action plans, independent of other components of asthma education.

Systematic Review of the Evidence

The following description of the SRE is an adaptation of the evidence report, including direct excerpts, submitted by the Blue Cross Blue Shield Association Evidence-Based Practice Center. (See Introduction, Methods.)

Methods of Literature Search

For the purpose of the SRE, an action plan is a written algorithm that identifies specific clinical indicators that should alert patients to make adjustments in their medications and provides specific instructions on how to make these adjustments. EPR-2 recommends the use of both a daily self-management plan and an action plan for exacerbations. Generally, studies included in the SRE involved the use of one plan that combined the objectives of both. Typically, the plans divided steps for patient actions into different zones, in which recommended actions are correlated with differing acute signs and symptoms of worsening asthma. Most of the plans in the available studies used four-zone plans, some were three-zone plans that did not include directions for use of oral corticosteroids before seeking emergency care.

The evidence review examined studies in which the intervention used an action plan as defined above and, if asthma education was given to both treatment and control groups, the treatment group had no more than 1 additional hour of education for the action plan. The treatment/observation duration was at least 12 weeks, and the intervention and control groups received the same treatment, except that the intervention group also received a written action plan. Studies were excluded if the comparisons were confounded by additional treatment components in the intervention group—for example, optimization of medications in the intervention group only or education programs of more than 1 hour in the intervention group only. The literature review included randomized controlled trials (RCTs) in which at least 25 evaluable patients (not physicians) were randomly allocated to the intervention and control groups.

Summary of Findings

Studies

Seven studies involving more than 1,400 patients met SRE inclusion criteria for review; only one of the studies included children. (See the key evidence tables in this section.) None of the studies met SRE standards for high quality; each had significant limitations. None was conducted with sufficient power (i.e., adequate numbers of subjects in each study arm) to enable comparisons between treatment and control groups. In one study reporting reduced emergency department visits, data were unavailable to control for baseline differences that may have existed between treatment and control groups, and the reported effect may be attributed to a subset of high frequency users. In another study, the design involved clinicians who both provided plans and collected assessment data. Moreover, a large number of subjects were excluded from the analyses.

All seven studies compared medical management with written action plans to medical management without written action plans, and all used a peak flow meter-based plan. Three of the studies also included similar but limited asthma education for both the intervention and control groups, but the groups still differed as to whether written plans were used. In two trials, the control group used peak flow meters but without an action plan.

Results of Studies

Five trials documented no differences in outcomes, and two trials documented significant benefit of written action plans, especially in reducing emergency department visits. However, there were notable limitations to each of these trials, as described earlier. In summary, SRE study data were insufficient to support or to refute the advantages of using asthma action plans independent of self-management education when compared with medical management alone.

Additional Literature/Information

Evidence supporting the use of written plans as a component of self-management education is reported in a recent Cochrane Collaboration review (Gibson et al. 2000). The SRE question on action plans provides a clearer assessment of isolating the advantages of providing an action plan. The Cochrane review centered on the benefits of self-management interventions and regular medical review with the clinician vs. usual medical care. The Cochrane review, however, also contrasted those self-management interventions with written action plans to those without written action plans. The review included some of the same studies included in the SRE but overcame the limitations of study sample sizes by pooling data. Further, the set of 25 studies in the Cochrane review was larger than the 7 in the SRE due to the broader question under review.
In the Cochrane analysis that compared results of self-management interventions with action plans to those without, the interventions with written action plans demonstrated the greatest benefits, including reduced asthma-related hospital admissions (odds ratio 0.35, 95 percent confidence interval) and reduced emergency department visits (odds ratio 0.55, 95 percent confidence interval). In addition, patients who managed their asthma by adjusting medications according to a written action plan had better lung function than those whose medications were adjusted by a doctor during regular care visits. The review concluded that training in asthma self-management that involves self-monitoring by either peak flow or symptoms, coupled with regular medical review and a written action plan, appears to improve health outcomes for adults with asthma.

Additional evidence supporting written action plans coupled with regular patient education and medical review is available from a recent case control study (Abramson et al. 2001). This study does not fit the SRE review criteria because studies that qualified for this review were required to be RCTs allowing inferences of cause and effect, and they were required to provide an action plan independent of a multicomponent intervention including education. Although the Abramson study is not an RCT, it is a well-conducted study that compared 51 patients who died from asthma to 202 patients presenting to hospitals with acute asthma. The study reported that written action plans for patients with severe persistent asthma were associated with a 70 percent reduction in mortality risk. As such, the study supports the opinion that providing written action plans as part of asthma education is an important element of practice.

Recommendations for EPR Update

No data from the SRE, in which RCTs compared written action plans to medical management alone, indicate the need to change the EPR-2 action plan recommendations (SRE-Evidence B). Additional data from studies on action plans as a part of self-management education support the EPR-2 recommendations (Evidence B, C). The following blue text indicates revisions that should be incorporated into the text on pages 33 and 123 in EPR-2.

Component 1: Measures of Assessment and Monitoring; Periodic Assessment and Monitoring (page 33 in EPR-2)

Whether peak flow monitoring, symptom monitoring, or a combination of approaches is used, the Expert Panel believes that self-monitoring is important to the effective self-management of asthma. The nature and intensity of self-monitoring should be individualized, based on such factors as asthma severity, patient's ability to perceive airflow obstruction, availability of peak flow meters, and patient preferences.

It is the opinion of the Expert Panel that, regardless of the type of monitoring used, patients should be given a written action plan and instructed to use it. (See figure 4–5.) It is the opinion of the Expert Panel that including action plans as part of an overall effort to educate patients in self-management is the soundest approach and is especially indicated for patients with moderate or severe persistent disease or a history of severe exacerbations (Evidence B, C). It is the opinion of the Expert Panel that a plan is important in large part because it enhances clinician-patient communication. The plan should define a regimen that meets the medical needs of the patient

and should have a format that facilitates the patient's understanding and ability to take appropriate action to control the disease. Regardless of format, an effective plan should include the following:

- Explicit, patient-spe[illegible] for environmenta[illegible] other [illegible]ive efforts that m[illegible]ry [illegible] or reduce the impact of exacerba[illegible]
- An [illegible]ithm of proc[illegible]at [illegible]bes how t[illegible] use long-term-c[illegible] medicines, give[illegible] of specifi[illegible]ances and conditions, [illegible]ear instruc[illegible] on how t[illegible] medicine adj[illegible] when conditions [illegible]
- Steps the patient s[illegible] take when [illegible]nes are ineffective or if an eme[illegible] situatio[illegible]
- Contacts for securing urge[illegible] if needed

As emphasized above, it is the opin[illegible] of the Expert Panel that a written action plan is consid[illegible] part of ongoing efforts to provide self-management education and support appropriate to the severity of the patient's asthma, the patient's age, and related circumstances (Evidence B, C). The clinician should periodically review the plan, revise it as necessary, and confirm that the patient knows what to do if his or her asthma gets worse.

Component 4: Education for a Partnership in Asthma Care, Key Points (page 123 in EPR-2)

- Patient education should begin at the time of diagnosis and be integrated into every step of clinical asthma care.
- It is essential that education be provided by all members of the health care team. The principal clinician should introduce the key educational messages and negotiate agreements with patients; these messages should be reinforced and expanded by all members of the health care team.
- Teach asthma self-management, tailoring the approach to the needs of each patient. Maintain a sensitivity to cultural beliefs and practices.
- Teach and reinforce at every opportunity:
  - Basic facts about asthma
  - Roles of medications
  - Skills: inhaler/spacer/holding chamber use, self-monitoring
  - Environmental control measures
  - When and how to take rescue actions.
- Jointly develop treatment goals.
- To encourage an active partnership, provide all patients with a written daily self-management plan and an action plan for exacerbations. A written action plan is considered part of ongoing efforts to provide self-management education and support appropriate to the severity of the [illegible] asthma, the patient's age, and re[illegible]stances (Evidence B, C). Action plans are especially important for patients with moderate-to-severe asthma and patients with a history of severe exacerbations. Provide appropriate patients with a daily asthma diary.
- Encourage adherence by promoting open communication; individualizing, reviewing, and adjusting plans as needed; emphasizing goals and outcomes; and encouraging family involvement.

[illegible]ommenda[illegible] Futu[illegible]ch

Research that may enhance the quality and effect of interventions fostering patient self-management would examine the following questions:

- Are some action plan formats more effective than others? What characterizes the most effective format?
- What alternative action plan formats are effective, given specific patient needs, including disease severity, literacy levels, languages spoken, ages, and unique management problems (e.g., comorbidities)?
- How much time and emphasis should be given to the development of action plans during the course of clinical counseling? In comprehensive education programs? In medical review?

- What are potential means of providing self-management interventions that include action planning to patients who are members of underserved populations (e.g., reaching them through worksites, community centers, or churches)?
- How effective are written action plans in treating children with asthma?
- How effective are written action plans in different caretaker situations (e.g., daycare, camps, or school)?

Key Evidence Tables

Table 2-1. Study Characteristics

Citation	Design	Study Setting	
Optimal medical management vs. [illegible]ment + peak flow meter (PFM)-based action plan			
Jones, Mullee, Middleton et al. 1995	Randomized; parallel, controlled	Country: United Kingdom Funding: Pharm. ind. grant Tx Setting: Primary/specialty combination, university Multicenter	
Drummond, Abdalla, Beattie et al. 1994 (GRASSIC)	Randomized; parallel, controlled	Country: United Kingdom Funding: Academic grant Tx Setting: Specialty care, nonuniversity Multicenter	
Ayres, Campbell, Follows 1995	Randomized; parallel, controlled	Country: United Kingdom Funding: Pharm. ind. grant Tx Setting: Unknown Multicenter	
Cowie, Revitt, Underwood et al. 1997	Randomized; parallel, controlled	Country: Canada Funding: Hospital Tx Setting: Primary/specialty combination, university Multicenter	
Cote, Cartier, Robichaud et al. 1997	Randomized; parallel, controlled	Country: Canada Funding: Pharm. ind. grant Tx Setting: Specialty care, nonuniversity Multicenter	
Optimal medical management + (PFM) use (without action plan) vs. optimal medic[illegible]agement + PF[illegible]ion plan			
Ignacio-Garcia and Gonzalez-Santos 1995	Randomized; parallel, controlled	Country: Spain Funding: Not specified Tx Setting: Specialty care, nonuniversity	
Charlton, Antoniou, Atkinson et al. 1994	Randomized; parallel, controlled	Country: Australia Funding: Pharm. ind. and government and university funding Tx Setting: Specialty care, nonuniversity	

	Eligibility	Comments
	Patient eligibility based on symptoms only Included patients using inhaled corticosteroids <1,000 mcg per day for at least 1 month Exclusions: Patients on oral steroids or using peak flow meters at home	Power based on several outcomes (FEV needed 23 patients, sixfold reduction in night wakening needed 21 per group, eightfold reduction in days off work or school needed 37 per group). 2-week course of oral steroids given before randomization to optimize lung function.
	Patient eligibility based on lung function and utilization Inclusion: FEV_1 reversibility 20% or greater Exclusion: Patients who already owned a PFM	Power based on the 569 randomized, but n varies for each outcome and in some cases is not specified as to exact n, just that n was > = 250; may not be powered for all outcomes. Patients included had less severe asthma on entry than those who already owned a PFM and were excluded, especially with regard to social and physical functioning.
	Patient eligibility based on lung function, symptoms, utilization Inclusions: PEF variability maximum 0.15%; nights/week with symptoms minimum 3; use of inhaled corticosteroids or sodium cromoglycate for a minimum of 3 months	Doctor also graded the overall and individual severity of symptoms as 0 = none and 3 = severe.
	Patient eligibility based on symptoms and utilization Inclusions: Treatment for an exacerbation of asthma in an ER or attending a university asthma clinic; history of receiving urgent treatment for asthma in the previous 12 months	Subjects were recruited by contacting those who had been treated for an exacerbation of asthma in an emergency room or those attending a university asthma clinic who had a history of having received urgent treatment for their asthma in the previous 12 months.
	Patient eligibility based on lung function and symptoms FEV_1 postbronchodilator 85–100% of predicted PEF minimum 85% of predicted; PEF variability minimum 0%; Methacholine Exclusion: Patients having previously taken part in an asthma educational program	In discussion "although the control group received more than the usual care treatment, none received book, none had written action plan; none had structured education or PFM at home after run-in." Run-in = 2–6 wks.; diagnosis of asthma included need to take daily anti-inflammatory agents; were excluded.
	Patient eligibility based on utilization only Inclusion: Patients from outpatient asthma clinic with asthma for 2 years	One doctor aware of the group assignment was responsible for assessment of all patients' condition, but the paper also says "in control group, the doctor assessing the patient was blinded with regard to registers of peak flow monitoring until end of study", random allocation by order of recruitment.
	Patient eligibility based on utilization only Inclusion: Patients who required admission for asthma or attended the outpatient department	Randomization was based on age, sex, whether they used asthma prophylaxis before study.

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44. AHRQ Publication No. 01–E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Table 2-2. Lung Function Outcomes: FEV_1

Citation	Study Arm	Number Enrolled	Number Evaluable	Treatment Duration (weeks)	
Usual care vs. peak flow meter action plan					
Jones, Mullee, Middleton et al. 1995	Usual care	64	39	26	
	PFM-based action plan	63	33	26	
Drummond, Abdalla, Beattie et al. 1994 (GRASSIC)	Usual care	284	260	52	
	PFM-based action plan	285	250	52	
Ayres, Campbell, Follows 1995	Usual care	64	64	24	
	PFM-based action plan	61	31	24	
Cowie, Revitt, Underwood et al. 1997	Usual care	48			
	PFM-based action plan	46			
Cote, Cartier, Robichaud et al. 1997	Usual care	54			
	PFM-based action plan	50			
Usual care + PFM use alone vs. usual care + PFM-based action plan					
Ignacio-Garcia and Gonzalez-Santo 1995	Usual care + PFM use	44	35	28	
	Usual care + PFM-based action plan	50	35	28	
Charlton, Antoniou, Atkinson et al. 1994	Usual care + PFM use	43			
	Usual care + PFM-based action plan	48			

	Baseline FEV_1*	FEV_1	P-Value	P-Value Comparison	Comments
	85.4 +/- 17.5 % of predicted	81.2 +/- 18.3 % of predicted			
	87.1 +/- 16.9 % of predicted	83.2 +/- 18 % of predicted	NS	Absolute value, Tx vs. Ctl	
	78.1 % of predicted	75.4 +/- 27.7 % of predicted			95% CI for baseline FEV is 74.8-81.4.
	77.3 % of predicted	74.6 +/- 27.8 % of predicted	NS	Change, Tx vs. Ctl	95% CI for baseline FEV is 74.1-80.5.
	2 +/- 0.1 L (type predose)	2.2 +/- 0.1 L (type predose)			Unclear number of patients analyzed on each end point.
	2.3 +/- 0.1 L (type predose)	2.3 +/- 0.2 L (type predose)	NS	Absolute value, Tx vs. Ctl	Unclear number of patients analyzed on each end point.
	78 +/- 21.3 % of predicted				Number of subjects with <60% predicted was 10.
	82 +/- 20.5 % of predicted				Number of subjects with <60% predicted was 9.
	65.34 +/- 16.6 % of predicted (type predose)	65.48 +/- 24.7 % of predicted			
	69.03 +/- 24.0 % of predicted (type predose)	80.45 +/- 23.3 % of predicted	<0.0040	Absolute value, Tx vs. Ctl	

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44. AHRQ Publication No. 01-E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Table 2-3. Symptom Score Outcomes

Citation	Study Arm	[illegible]	Number Evaluable	Treatment Duration (weeks)	Baseline Daytime Symptom Score	Final Daytime Symptom Score	
Usual care vs. peak flow m[illegible] a[illegible]							
Jones, Mullee, Middleton et al. 1995	Usual care	64	45	26		4.95 (median; scale, 0-3)	
	PFM-based action plan	63	39	26		2.85 (median; scale, 0-3)	
Drummond, Abdalla, Beattie et al. 1994 (GRASSIC)	Usual care	284	67	52			
	PFM-based action plan	285	54	52			
Ayres, Campbell, Follows 1995	Usual care	64	64	24	1.91 +/- 0.6 (scale, 0-3)	1.39 +/- 1.11, (scale 0-3)	
	PFM-based action plan	61	61	24	1.77 +/- 0.6 (scale, 0-3)	1.38 +/- 0.12 (scale, 0-3)	
Cowie, Revitt, Underwood et al. 1997	Usual care	48	48	24			
	PFM-based action plan	46	46	24			
Cote, Cartier, Robichaud et al. 1997	Usual care	54					
	PFM-based action plan	50					
Usual care + PFM use alone vs. usual care + PFM-based action plan							
Ignacio-Garcia and Gonzalez-Santos 1995	Usual care + PFM use	44	35	28			
	Usual care + PFM-based action plan	50	35	28			
Charlton, Antoniou, Atkinson et al. 1994	Usual care + PFM use	43	37	52		0.22 (median; scale, 0-3)	
	Usual care + PFM-based action plan	48	42	52		0.26 (median; scale, 0-3)	

	P-Value	Final Nighttime Symptom	P-Value	Comments
		0.75 (median; scale, 0-3)		Symptom score across study was divided by number of days w/diary data X 28 to give a monthly rate; sx score day = cough; sx score night = wakening at night; median wheeze = 5.46; shortness of breath = 7.88; asthma restricting normal daily activities = 0.0
	NS[1]	0.35 (median; scale, 0-3)	NS[1]	Symptom score across study was divided by number of days w/diary data X 28 to give a monthly rate; sx score day = cough; sx score night = wakenings at night; median wheeze = 4.39; shortness of breath = 6.50; asthma restricting normal daily activities = 0.17.
				Night and day sx score outcome is only from a subgroup of patients reporting variation in outcome; 112/246 never reported sleep disturbances; 15/246 reported that their sleep was disturbed every night.
				Night and day outcome is only from a subgroup of patients reporting variation in outcome, controlled for peak flow, FEV_1, duration of asthma; 114/239 never reported sleep disturbances; 14/239 reported that their sleep was disturbed every night.
		0.69 +/- 0.13, (scale 0-3)		Sx score day = overall severity of asthma. Changes in: sleep disturbance scores 1.89 → 0.69; cough at rest 1.08 → 0.69; wheeze at rest was 1.25 → 0.67; difficulty breathing 1.47 → 0.96; cough with activity = 1.75 → 1.30.
	NS[1]	0.67 +/- 0.14 (scale, 0-3)		Sx score day = overall severity of asthma. Changes in: sleep disturbance scores 1.79 → 0.67; cough at rest 1.00 → 0.87; wheeze at rest was 0.97 → 0.74; difficulty breathing 1.41 → 0.85; cough with activity = 1.48 → 1.28. All comparisons in sx scores between groups NS.
				No significant differences in other indexes of asthma control, including waking with asthma, $beta_2$-agonist use, or self-rating of asthma severity differed among the groups at 3 months or at 6 months after entry.
				No significant differences in other indexes of asthma control, including waking with asthma, $beta_2$-agonist use, or self-rating of asthma severity among the groups at 3 months or at 6 months after entry.
				Nighttime symptoms = total nighttime awakenings over total study. (Values not reported by AHRQ)
				Nighttime symptoms = total nighttime awakenings over total study.
		0.25 (median; scale, 0-3)		Sx score day = wheeze day; Sx score night = wheeze night; daily score for activity restriction was 0.13.
	NS[1]	0.15 (median; scale, 0-3)	NS[1]	Sx score day = wheeze day; Sx score night = wheeze night; daily score for activity restriction was 0.06, p <0.05 compared to control.

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44. AHRQ Publication No. 01–E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

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